Haemophilus influenzae type b

Haemophilus influenzae type b is a disease that most health care providers will never see again. It was not so long ago that the disease was frightfully common. Then a vaccine came and we stopped seeing kids with Hib meningitis. No one that I know misses it a bit. The Hib chapter in your text begins on page 101 if you want to follow along.

Haemophilus influenzae type b, or Hib, was once the leading cause of bacterial meningitis among children less than 5 years old. Approximately 1 in 200 children developed some form of invasive Hib disease. Almost all invasive infections were among children less than 5 years of age.

Haemophilus influenzae was first described by Robert Pfeiffer in 1892 in the sputum of patients with influenza, so he believed that this bacteria was the CAUSE of influenza. Influenza is actually caused by a virus, but that was not known until 1933. In the 1930s, Margaret Pittman defined the microbiology of Haemophilus including the importance of the capsular polysaccharide. The polysaccharide was not purified and characterized until the 1970s. The first vaccine was licensed in 1985 and the first conjugate vaccine was licensed in 1987. With widespread use of conjugate vaccines, invasive Hib disease is now rarely seen.

Haemophilus influenzae is an **aerobic gram negative bacterium**. The **polysaccharide capsule** is responsible for the organisms' virulence, and for immunity to it. There are **6 different serotypes of polysaccharide capsule, designated as A through F**. There are also nontypable strains that colonize the respiratory tract and are a major cause of otitis media and bronchitis. But 95% of invasive disease is caused by type b so we will focus solely on it. Some people are colonized with Hib without ill effects. Unfortunately, SOME of these colonized people develop INVASIVE disease. What triggers invasive disease is not well understood, but it may be something as minor as an upper respiratory infection.

Hib invasive disease can affect many different organ systems. This pie chart shows the different clinical manifestations of invasive Hib disease. As you can see, Hib can cause **bacteremia**, can infect skin as **cellulitis**, the joints as **septic arthritis**, and the bones as **osteomyelitis**. It can also cause **pneumonia**. Fifteen to twenty percent of invasive Hib disease was **epiglottitis**- inflammation of a tissue flap at the opening of the airway. But by far the most common clinical manifestation was **meningitis**. Meningitis accounted for **50% to 65% of cases of invasive Hib disease**. Hib was the most common type of bacterial meningitis in infants. **Hearing impairment or neurologic sequelae occurred in 15% to 30%** of survivors. The **case fatality rate was 2% to 5% even with effective antimicrobial therapy**.

With the disappearance of Hib meningitis, *Streptococcus pneumoniae*, or pneumococcus, has become the most common cause of bacterial meningitis in infants. Pneumococcal meningitis has not become more common. But since Hib meningitis now rarely occurs, what was Number 2 has become Number 1 just by default.

Haemophilus influenzae is a **human disease**, and the **reservoir** is infected humans who are usually asymptomatic. The epidemiology of Hib disease is complex because of transmission from asymptomatic carriers. In the prevaccine era, studies suggested that 5% to 15% of children were colonized at any given time. Carriage could persist for months. Most children were infected by the age of 5 and, presumably, developed immunity to the bacteria from these subclinical infections. **Respiratory transmission** of Hib occurs through the spread of infected droplets. **Communicability of Hib is limited**. Secondary clinical cases are unusual, but communicability may be higher in some circumstances, such as close contact with a symptomatic case in day care.

Invasive Hib disease became nationally reportable in 1991, so historical data before that is estimated. Before an effective vaccine became available, there were an estimated 20,000 invasive Hib infections each year, with up to 1,000 deaths. This is a graph of the incidence of invasive Hib since 1987. The rate per 100,000 children less than 5 years of age is shown along the vertical axis and the year on the horizontal axis. Incidence was estimated between 25 and 60 cases per 100,000 in the prevaccination era. The rate of Hib invasive disease began to drop soon after the first conjugate vaccines were licensed in 1987, and have continued to drop to the present. From 1998 through 2000, only 197 confirmed Hib cases were reported among children younger than 5 years of age, an average of about 66 cases per year. This is a rate of 0.3 per 100,000 children per year. Of these 197 children with invasive Hib disease, 44% were less than 6 months of age, so they were too young to have completed the 2 or 3 dose primary Hib vaccination series. Of the 111 children who were 6 months of age or older, about one third – about 13 children per year – had received a complete primary series, and some had received a booster dose at 12 to 15 months of age. The cause or risk factors of these apparent vaccine failures is not known. Fourteen children died as a result of invasive Hib disease in 1998 through 2000. 80% of these children were less than 6 months of age. Of the older children, none had received a complete series of Hib vaccine. In 2002, only 34 invasive Hib cases were reported among children less than 5 years of age.

So – although Hib vaccine failure can occur, the majority of children who develop invasive Hib disease were among children too young to be vaccinated, or older children who were incompletely vaccinated.

The first Hib vaccine was licensed in 1985. It was purified Hib polysaccharide. Polysaccharides are not very immunogenic- they do not stimulate the immune system very well. As a result, polysaccharide vaccines are not effective, including the first Hib vaccine, in children younger than 12 months of age, and the

effectiveness in older children is variable. This is a serious problem if the disease you wish to prevent occurs in infants. The limited effectiveness of polysaccharide Hib vaccine was improved by a process known as conjugation. The idea is to link a poor antigen, the polysaccharide, to a good one, a protein. **Conjugation enhances antibody production**, especially in young children. **Repeat doses elicit a booster response**, so antibody titers go up with every dose. And the **antibody that is produced has increased biologic activity**- which means it works better. What happens with conjugation is that the protein polysacchide complex elicits a T cell dependent response. That means that T cells become involved in the immune response, instead of the T independent response characteristic of pure polysaccharide. The original pure polysaccharide Hib vaccine is no longer produced. Only conjugated polysaccharide Hib vaccines are available now in the United States.

There are **3 conjugate vaccines licensed for use in infants**. All 3 are **chemically and immunologically different**. However, available data suggests **3 doses of any combination of them confers protection**. Here is the list of available Hib vaccines. **HBOC** is marketed as Hibtiter. **PRP-T** is marketed as ActHIB, and is included in the combination Trihibit. **PRP-OMP** is marketed as PedvaxHIB, and is included in the combination COMVAX. We will talk more about the combination vaccines a little later. One additional conjugate Hib vaccine not shown on that slide is PRP-D, trade name ProHIBIT. This particular conjugate vaccine was not immunogenic in INFANTS. ProHIBIT is no longer distributed in the United States.

HIB vaccination should be started for all infants, including premature infants, at 2 months of age. Hib vaccine can and should be administered simultaneously with all other childhood vaccines. A primary infant series of HIB vaccine consists of 2 or 3 doses, depending on the vaccine. **HBOC**- Hibtiter- and **PRP-T**- ActHib- have a three dose primary series, at 2, 4, and 6 months of age. **PRP-OMP**, or PedvaxHib, has a two dose schedule, at 2 and 4 months. A dose of PedvaxHib at 6 months is not required. For all three vaccines, a booster dose should be given at 12 to 15 months of age. The minimum age for the last dose of the Hib series is 12 months. The **first dose of Hib vaccine is usually administered at 2 months of age**, but may be given as early as 6 weeks. Available data suggest that **vaccination at less than 6 weeks of age may induce what is known as immunologic tolerance to Hib antigen**. That means that doses given before 6 weeks of age may cause the child to be incapable of responding to subsequent doses. That is not a good thing. Based on limited data, it appears that the earlier in life the vaccine is given, the more likely that tolerance will occur. So the **minimum age for ALL Hib vaccines is 6 weeks**. The first two or three doses of the series should be separated by 2 months, but a minimum interval of 4 weeks may be used if an accelerated schedule is needed. The booster dose should be given on or after the first birthday, and should be separated from the preceding dose by at least 2 months.

Children younger than 2 years of age do not reliably develop immunity following invasive Hib disease. So these children should be vaccinated as usual after they recover.

There are times when you encounter a child who received Hib vaccine from another office or clinic. You may not know or may not stock the Hib vaccine the child received for the earlier doses. Fortunately, studies have shown that excellent immune responses are achieved when different brands of Hib vaccine are interchanged in the primary series. So ACIP recommends that **all conjugate HIB vaccines be considered completely interchangeable, for both the primary series and the booster dose**. However, **3 doses should be given as the primary series if more than one brand of vaccine is used**. In particular, if Merck's vaccine – PedvaxHib – is given in a series with one of the other two products, the child should receive 3 doses and a booster, not 2 doses and a booster. It should not happen, but sometimes children are late getting started with the vaccination schedule, including Hib. If the child gets started before 7 months of age, they should receive the full primary series of 2 or 3 doses, depending on the vaccine you are using. But unvaccinated **children 7 months of age or older starting the series late may not need the entire 3 or 4 dose series**. The number of doses a PREVIOUSLY UNVACCINATED child needs **depends on their current age**- the age at which the series is being started. **Unvaccinated children 15 to 59 months of age need only 1 dose** of any licensed conjugate vaccine. A table outlining the number of Hib doses by the age at the first dose is on page 108 of the text. A careful reader noticed that we inadvertently omitted an important bit of information from this table. If you have your book, please turn to the table now. Follow the booster column down to the PRP-OMP 12 to 14 month row. Notice that this cell of the table contains a faint dash. This is the error. This cell SHOULD say "**2 months later**". Please write this into the cell now. A child with one dose of PedvaxHib administered at 12 to 14 months of age needs a booster dose 2 months after the first dose. We apologize for this error and will fix it in the next edition.

A more common situation is when a child has received one or two doses of Hib vaccine on schedule, but has since fallen behind. This is referred to as a lapsed series. These situations are similar to those when the child is late starting the schedule. Depending on the child's age now, he or she may not need a full series of 3 or 4 doses. You can use the catch-up schedule to figure out how many, if any, additional doses of Hib vaccine a child may need. Here is the catch-up schedule. It is included in your book in Appendix A, on page A2. If you have your book, please turn to it now. This part of the catch-up schedule tends to confuse people, so I would like to work through an example with you. Suppose you have a 14 month old child in your office who has a record of one dose of Hib conjugate vaccine at 6 months of age. The first question is whether the child needs any more doses of Hib vaccine. To determine this, go to the Dose 1 to Dose 2 column and follow it down to the Hib row. There are three entries in the Hib row in this column. The one that applies here is the first one. Your patient received his first and only dose at 6 months of age. A second dose is needed a minimum of 4 weeks after the first if the first dose was administered at less than 12 months of age. Since the minimum interval has elapsed, you should give the second

dose today. Next question: does the child need a third dose. To determine this, you move to the next column, labeled Dose 2 to Dose 3. Follow this column down to the Hib row. There are also 3 entries in this cell. Reading through them, you find the one applicable to your patient is the second entry: if current age is 12 months or older, AND the second dose was given at age less than 15 months, then a third and final dose is recommended at least 8 weeks after the dose you gave today. So you make the child a return appointment for 2 months for the third dose of Hib. And make sure the parent understands the importance of returning for this, and the other vaccines the child needs.

There is a Hib lapsed schedule table on page 109 of your book that was adapted from the 2000 edition of the AAP Red Book. It has the same information as the catch-up schedule. But the catch-up schedule has the advantage of including lapsed or late start schedules for other vaccines as well as Hib.

Another Hib vaccine issue that we frequently receive questions about is vaccination of older children and adults. Hib vaccination is **generally not recommended for persons older than 59 months of age** because there is very little Hib disease in older persons. Presumably, this lack of disease in older children and adults is because of immunity acquired through asymptomatic infection as children. Although none of the current Hib vaccines are specifically approved for this indication, ACIP recommends that Hib vaccination be **considered for certain high risk older children and adults**. This would generally include persons with anatomic **asplenia** (those who have had their spleen removed), or functional asplenia (those whose spleen is not functional, such as children with sickle cell disease). Vaccination can also be considered for persons with **immunodeficiency**, including HIV infection. Hib vaccine is recommended for all people who have received a **hematopoietic stem cell transplant**. Older children and adults who are at high risk of Hib disease should receive only **one pediatric dose of any Hib conjugate**. Now that we have discussed the specifics of the use of single antigen Hib vaccines, let's move on to combination vaccines that contain Hib.

The first combination vaccine to include conjugate Hib vaccine was licensed in 1993. Since then, 3 additional combinations that include Hib have been approved for use. Two of these combination vaccines contained whole cell pertussis vaccine, and are no longer available in the United States. Two combination vaccines that include Hib are currently available. There is a **hepatitis B-Hib combination, COMVAX**. We will come back to COMVAX in a moment. There is also one licensed **DTaP-Hib combination vaccine, Trihibit**. Trihibit is **ActHib reconstituted with Aventis Pasteur's DTaP vaccine, Tripedia**. This vaccine can be **used for the last dose of the DTaP-Hib series ONLY**. Trihibit is not approved by FDA for the primary series at 2, 4, or 6 months because of evidence that the immunogenicity of the Hib component is reduced when it is mixed with DTaP. The currently licensed TriHIBit **should not be used for the first three doses of the series** regardless of the child's age. You may encounter children who received TriHIBit for one or more of the first three doses of the series. If so, **the primary series Hib doses given as TriHIBit should be disregarded**. You

can count the DTaP doses as valid. You should **revaccinate the child with single antigen Hib vaccine appropriate for their age**. You may need to use the catch-up schedule to determine how many doses of single antigen Hib the child needs. This conservative approach assures that the child is truly protected against invasive Hib disease. We also receive many questions about the use of Trihibit as the last dose of the Hib series when a different brand of Hib vaccine was used for the primary series. The Hib footnote of the childhood schedule helps clarify this situation. Although not in the package insert, ACIP recommends that while Trihibit cannot be used for the primary series, it **may be used as the booster, or final, dose following any Hib vaccine series**, including a Comvax primary series. So to use Trihibit the child must be at least 12 months of age and have received at least one prior dose of Hib vaccine. **Trihibit should NOT be used if the child has received no prior Hib doses** regardless of their current age.

Another combination vaccine that contains Hib is **Comvax**. Comvax is a **hepatitis B Hib combination**. It contains a standard dose of PedvaxHib, and standard 5 microgram pediatric dose of Merck's hepatitis B vaccine, Recombivax HB. As with other combinations, the vaccine can be **used when either antigen is indicated and the other component or components are not contraindicated**. As we discussed earlier, Hib vaccine **should not be given to infants less than six weeks of age** because of the potential of immune tolerance to HIB. So Comvax also cannot be used in infants less than six weeks of age. That means it cannot be used when an infant receives hepatitis B vaccine at birth or at one month of age. Comvax is not **approved for use when the infant's mother is hepatitis B surface antigen positive**. However, in 1997, ACIP recommended that Comvax could be used to complete the series for high risk infants as well as all other infants. We will discuss this further during the hepatitis B segment later in the course. Since Comvax contains Merck's PedvaxHib, the routine schedule is 3 doses, at 2, 4, and 12 months of age. If a child has received a birth dose of hepatitis B vaccine, Comvax may still be given at 2, 4, and 12 months of age. But since the child does not need the hepatitis B component at 4 months of age, an alternative would be to give single antigen PedvaxHib at 4 months, then Comvax at 12 months. Also – remember that if more than one BRAND of Hib vaccine is given, the child needs three doses and a booster after the first birthday. So if a child gets COMVAX at 2 months, then you switch to ActHib at 4 months, a third dose is recommended at 6 months of age, and a booster after the first birthday. Likewise, if the child starts with ActHib at 2 months, then gets COMVAX at 4 months, a third dose should be given at 6 months, with a booster dose after the first birthday.

Adverse reactions following Hib vaccines are similar to those following other inactivated vaccines. But adverse reactions following Hib vaccine are remarkably mild. **Local adverse reactions**, such as swelling, redness, and pain, are reported in **5% to 30%** of recipients. These symptoms usually resolve within 24 hours. **Systemic reactions such as fever are infrequent** and **serious adverse reactions rare**. Since Hib vaccines are inactivated, contraindications and precautions are also predictable. As with all vaccines, a **severe allergic reaction to a vaccine component or following a prior dose** is a contraindication.

Moderate or severe acute illness is a precaution, and vaccination should be deferred until the acute illness improves. Because of the risk of immunologic tolerance, age less than 6 weeks is a contraindication to all Hib-containing vaccines.

So that is the story with *Haemophilus influenzae* type b. It is a great vaccine, and has practically eliminated Hib disease as a threat to infants in the United States.